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THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawing of the extract of Patent Application No.285/MAS/2002, dated 12/04/2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad Andhra Pradesh, India-500 016.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 6th day of August 2003
15th day of Sravana, 1925(Saka)

(K.M. VISWANATHAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OF[illegible]E BRANCH
GOVERNME[illegible]OF INDIA
Guna Comple[illegible]th Floor, Annex.II
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PRIORITY DOCUMENT
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Vide C.B.R. No. 34724 dt 12.04.02

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

1. (a) that we are in possession of an invention titled **Novel anhydrous crystalline polymorph Form-II of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1– piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid (Gatifloxacin).**
   (b) that the complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to us.
2. further declare that the inventors for the said invention are Chakilam Naga Raju, Vetukuri Venkata Naga Kali Vara Prasada Raju and Rapolu Rajesh Kumar. All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500 016, Andhra Pradesh.**
3. that we are the assignee of the true and first inventors
4. that our address for service in India is as follows;

   Dr. Chakilam Naga Raju,
   Director (R&D),
   Dr. Reddy's Laboratories Limited,
   7-1-27, Ameerpet.
   Hyderabad, A.P., 500 016

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed)_____
Chakilam Naga Raju,
12-10-336/15/1,
Seethaphal Mandi,
Secunderabad – 500 061.

(Signed)_____
Vetukuri Venkata Naga Kali Vara Prasada Raju,
H.I.G: 401, VI Phase,
K.P.H.B. Colony,
Hyderabad-500 072.

(Signed) Rajeshkumar.R.
Rapolu Rajesh Kumar
Post: Cherlapally,
Mandal & Dist: Nalgonda – 508 001.

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application
7. following are the attachments with the application
   (a) complete specification (--19-- pages, in triplicate)
   (b) abstract of the invention (--01-- page, in triplicate)
   (c) drawings (--03-- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in bank draft bearing No. 995705 dated 11/04/2002 drawn on SBI, Jeedimetla Ind. Area Branch.

We request that a patent may be granted to us for the said invention

Dated this 10th day of April 2002.

(Signed)
Dr. Chakilam Naga Raju,
Director (R&D),
Dr. Reddy's Laboratories Limited.

To, The Controller of Patents
The Patents Office Branch, Chennai.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

Novel anhydrous Crystalline Polymorph Form-II of 1 – Cyclopropyl – 6 – fluoro – 8– Methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 - dihydroquinoline –3 – carboxylic acid (Gatifloxacin)

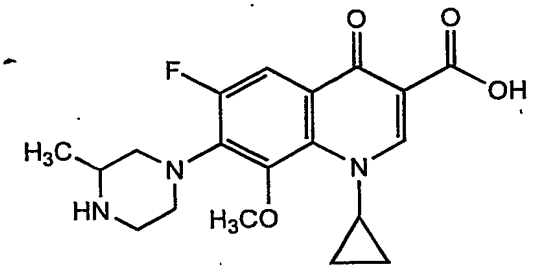
Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to the novel anhydrous crystalline form of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid. It is generically known as Gatifloxacin and marketed under brand name "Tequin".

The present invention also relates to method of making the anhydrous form of Gatifloxain, which can be depicted as Formula (1).



Formula (1)

Gatifloxacin and its pharmaceutically acceptable salts are useful as antibiotics.

BACK GROUND OF THE INVENTION

Quinolone carboxylic acid derivatives constitute a class of extremely potent and orally active broad-spectrum antibacterial agents. Several structural activity relationship (SAR) and quantitative structure activity relationship (QSAR) studies have led to the discovery of important class of quinolines called fluoroquinolones.

Gatifloxacin of Formula (1) belonging to the class of the said fluoroquinolones is significantly noted because of not only its potent antibacterial activity but also higher selectivity against bacteria from mammalian cells, which brings on an excellent selective toxicity.

Gatifloxacin is administered orally and intravenously. The usual dose of Gatifloxacin is 400mg once daily.

Several references disclosed the structure of Gatifloxacin and **USP 4,980,470;** incorporated here in by reference, describe the synthesis of Gatifloxacin hemihydrate. Gatifloxacin hemihydrate is prepared by condensing 1-cyclopropyl-6, 7- difluoro-1, 4-dihydro-4-oxo-8-methoxy quinoline-3-carboxylic acid with 2-methyl piperezine in DMSO, accompanied by chromatographic purification. The invention also includes the process for the preparation of various piperazine derivatives and their different salts, which are useful as antibacterial agents.

US 5,880,283 disclosed preparation of the Gatifloxacin sesquihydrate, which involves heating the mixture of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1– piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid with water, preferably 3-5 times over the weight of reactant at 80-85^{O}C and subsequent filtration and drying resulting in the sesqui hydrate of Gatifloxacin.

Japanese unexamined patent publication 63-198664, discloses Gatifloxacin hydrochloride salt is disclosed. The patent stated that hemihydrate and hydrochloride of Gatifloxacin is unstable due to their hygroscopic nature of the drug substance, and the problems are encountered due to its poor disintegration and dissolution rate while formulating the tablets.

The present invention is directed to anhydrous form of Gatifloxacin, which is non-hygroscopic, crystalline and non-solvated, generally, the hygroscopic nature will results due

to the presence of impurities, but the present inventive substance is non-hygroscopic, which infers the high purity of the compound. The present inventive substance has produced in non-solvated form, i.e., the content of residual solvents are well within the limits as per ICH guidelines; hence it is very well suited for pharmaceutical formulations.

The crystalline form of Gatifloxacin obtained as per procedure mentioned in our co-pending Indian Patent application (Sent to IPO, Chennai on 05.04.2002) is designated as anhydrous crystalline polymorph Form-I of Gatifloxacin.

The present invention of anhydrous crystalline form of Gatifloxacin is designated as polymorph Form-II of Gatifloxacin, herein after it is referred as polymorph Form-II.

The X-ray diffractogram pattern of polymorph Form-II of Gatifloxacin is different to the X-ray diffractogram pattern of earlier disclosed polymorph Form-I of Gatifloxacin.

The present invention of anhydrous crystalline polymorph Form-II of Gatifloxacin is having moisture content from 0.05% to 2.0% by KF and as per thermo gravimetric analysis, which is less than the hemi hydrate.

The crystalline nature of the present anhydrous inventive substance is characterized by its X-ray diffractogram, Differential Scanning colorimetry thermogram and IR spectrum.

Hence, the objective of the present invention is to provide a novel anhydrous crystalline polymorph Form-II of Gatifloxacin.

Another objective of the present invention is to provide a process for the preparation of anhydrous crystalline polymorph Form-II of Gatifloxacin, which is cost effective, commercially viable and well suited for industrial scale up.

SUMMARY OF THE INVENTION

The present invention is directed to novel anhydrous crystalline polymorph Form-II of Gatifloxacin. The present invention also provides the process for the preparation of anhydrous crystalline polymorph Form-II of Gatifloxacin, which comprises the azeotropic removal of water from hydrated form of Gatifloxacin at reflux temperature using an aliphatic hydrocarbon solvent such as cyclohexane. The process is commercially viable and well suited for industrial scale up.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig. 1 is a diagram showing the results of X-ray diffraction of the inventive substance.

Fig. 2 is a diagram showing the results of DSC of the inventive substance.

Fig. 3 is a diagram showing the results of IR spectrum of the inventive substance.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the novel anhydrous crystalline polymorph Form-II of Gatifloxacin of Formula (1) and a process for the preparation thereof.

The crystalline nature of novel anhydrous polymorph Form-II of Gatifloxacin of present invention may be characterized by its X-ray diffractogram, Differential Scanning colorimetry thermogram and IR spectrum.

The anhydrous nature of the inventive substance was characterized by its thermo gravimetric analysis, and the anhydrous nature of the compound was also confirmed by calculating the water content present in the compound by Karl Fischer (KF) method.

The present inventive substance is having a moisture content of 0.48% by KF method, which confirms the anhydrous nature of the compound.

The X-ray powder diffraction pattern of anhydrous crystalline polymorph Form-II was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The anhydrous crystalline polymorph Form-II of Gatifloxacin has X-ray powder diffraction pattern essentially as shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of the 2 theta (degrees), and percentage of intensity (in %).

Table-1:

2 theta (^{O})	**Intensity (I/I_O)**
5.931	100
14.116	68.5
22.509	33.7
21.073	31.3
15.833	20.7
27.571	15.9
27.807	15.6
11.248	13.0
12.426	10.2
23.249	9.2
11.906	8.6
24.287	8.0
29.389	6.2
21.507	4.7
24.943	4.3
17.991	3.7
19.646	3.2
18.667	3.0
39.841	2.3
26.918	2.3
28.504	2.2
16.276	2.2

The present invention of anhydrous crystalline polymorph Form-II of Gatifloxacin was characterized by its X-ray powder diffraction substantially as depicted in Figure (1).

The present invention provides the Differential Scanning Calorimetry thermogram of anhydrous crystalline polymorph Form-II of Gatifloxacin. The Differential Scanning Calorimetry thermogram exhibits a significant endo peak at 187.71^{O}C and substantially as depicted in Figure (2).

The present invention provides the Infrared data for anhydrous crystalline polymorph Form-II of Gatifloxacin, which was measured by KBr-transmission method with identified significant peaks at about 1620.9 and 1728.3 cm-^{1}.

The present invention provides the IR spectrum of anhydrous crystalline polymorph Form-II of Gatifloxacin substantially as depicted in Figure (3).

Another embodiment of the present invention is to provide the preparation of novel anhydrous crystalline form of Gatifloxacin, which comprises;

i) refluxing azeotropically the hydrated form of Gatifloxacin in water-immiscible aliphatic hydrocarbon solvent such as cyclohexane;

ii) cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii) isolating the solid obtained in step (ii) by conventional methods;

iv) drying of the isolated compound of step (iii) with/without vacuum at 30-70^{O}C, preferably 40-50^{O}C to afford anhydrous crystalline polymorph Form-II of Gatifloxacin.

Thus, the present invention is directed to a novel anhydrous crystalline polymorph Form-II of Gatifloxacin, which is non-hygroscopic, with residual solvents within permissible limits, which renders it well suited for pharmaceutical formulations.

The present invention will be explained in more detail with following examples but don't limit it in any way.

REFERENCE EXAMPLE:

Preparation of hydrated form of Gatifloxacin:

1-cyclo-6, 7-difluoro-1, 4-dihydro-4-oxo-8-methoxy quinolone-3-carboxylic acid (100 grams 0.339 moles) and 2-metyl piperazine (100 grams 1.0 mole) was added to Acetonitrile (500 ml) and the reaction mixture was slowly heated to the reflux temperature and stirred till the reaction was substantially complete. Then the solvent was distilled off completely and water (300 ml) was added to the residual mass and cooled the reaction mass to the temperature of 40-50^{O}C. The P^{H} was adjusted towards acidic with Acetic acid (250 ml). The mass was filtered off and then P^{H} of the filtrate was further adjusted to 6.0-8.0 with ammonia. The reaction mixture was cooled to a temperature of 10-15 ^{O}C and stirred for 30-45 minutes. Thus, the obtained solid was successively recrystallized to afford Gatifloxacin; which had a moisture content ranging from 2.5 to 50.0%.

EXAMPLE – 1:

Preparation of anhydrous crystalline polymorph Form-II of Gatifloxacin:

Gatifloxacin hydrate (10 grams, 0.026 moles, prepared as per reference example) was suspended in cyclohexane (50 ml) and heated to reflux to the temperature of 70-80^{O}C. Water was azeotropically removed, accompanied by cooling of the reaction mixture to 0-10^{O}C under stirring for 30-60 minutes to crystallize the solid mass. The crystallized solid mass was filtered, washed with cyclohexane (10 ml) and dried under reduced pressure at a temperature of 40-50^{O}C to constant weight.

(Weight: 9 grams, 90.0%, M.C. by KF is 0.48% and Purity: 99.58%).

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig: 1 is characteristic X-ray powder diffraction pattern of the novel anhydrous crystalline polymorph Form-II of Gatifloxacin.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2 theta values (in degrees) obtained are 5.931, 11.248, 11.906, 12.426, 14.116, 15.833, 1620.9, 17.991, 18.667, 19.646, 21.073, 21.507, 22.509, 23.249, 24.287, 24.943, 26.918, 27.571, 27.807, 28.504, 28.389 and 39.841 degrees two theta.

Fig: 2 is characteristic Differential Scanning Calorimetric thermogram of novel anhydrous crystalline polymorph Form-II of Gatifloxacin. The Differential Scanning Calorimetric thermogram exhibits a significant endo peak at 187.71^{O}C.

Vertical axis: Temperature (in ^{O}C); Horizontal axis: Signal (in mV).

Fig: 3 is characteristic Infra Red spectrum of anhydrous crystalline polymorph Form-II of Gatifloxacin with identified significant peaks at about 1620.9 and 1728.3 cm-^{1}.

Vertical axis: Wave length (in Cm^{-1}); Horizontal axis: Transmission (in %).

We claim:

1 A novel anhydrous crystalline polymorph Form-II of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy-7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid (Gatifloxacin).

2. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 1 has X-ray powder diffraction pattern with peaks at 5.931, 11.248, 11.906, 12.426, 14.116, 15.833, 16.276, 17.991, 18.667, 19.646, 21.073, 21.507, 22.509, 23.249, 24.287, 24.943, 26.918, 27.571, 27.807, 28.504, 28.389, and 39.841 degrees two theta.

3. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 2 having an X-ray powder diffraction pattern substantially as depicted in Figure (1).
4. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 1 having a differential scanning colorimetry thermogram which exhibits a characteristic endo peak at 187.71^{O}C.
5. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 4 having a differential scanning colorimetry thermogram substantially as depicted in Figure (2).
6. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 1 having identified characteristic peaks at about 1620.9 and 1728.3 cm-^{1} in the Infra red Spectrum.
7. The anhydrous crystalline polymorph Form-II of Gatifloxacin of claim 6 having an Infra red Spectrum substantially as depicted in Figure (3).
8. A process for preparing the novel anhydrous crystalline polymorph Form-II of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid (Gatifloxacin), which comprises;
   i. refluxing azeotropically the hydrated form of Gatifloxacin in water-immiscible aliphatic hydrocarbon solvent such as cyclohexane;
   ii. cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;
   iii. isolating the solid obtained in step (ii) by conventional methods;
   iv. drying of the isolated compound of step (iii) with/without vacuum at a temperature of 30-70^{O}C, preferably 40-50^{O}C to afford anhydrous crystalline polymorph Form-II of Gatifloxacin.

9. A process according to claim 8 of step (i) where in the aliphatic hydrocarbon solvent is cyclohexane.

10. The process for the preparation of novel anhydrous crystalline polymorph Form-II of Gatifloxacin substantially as herein exemplified.

Dated this 10th day of April 2002

Signed)_____
Dr. Ch. Naga Raju,
Director (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

The present invention is directed to novel anhydrous crystalline polymorph Form-II of Gatifloxacin. The present invention also provides the process for the preparation of anhydrous crystalline polymorph Form-II of Gatifloxacin, which comprises the azeotropic removal of water from hydrated form of Gatifloxacin at reflux temperature using an aliphatic hydrocarbon solvent such as cyclohexane. The process is commercially viable and well suited for industrial scale up.

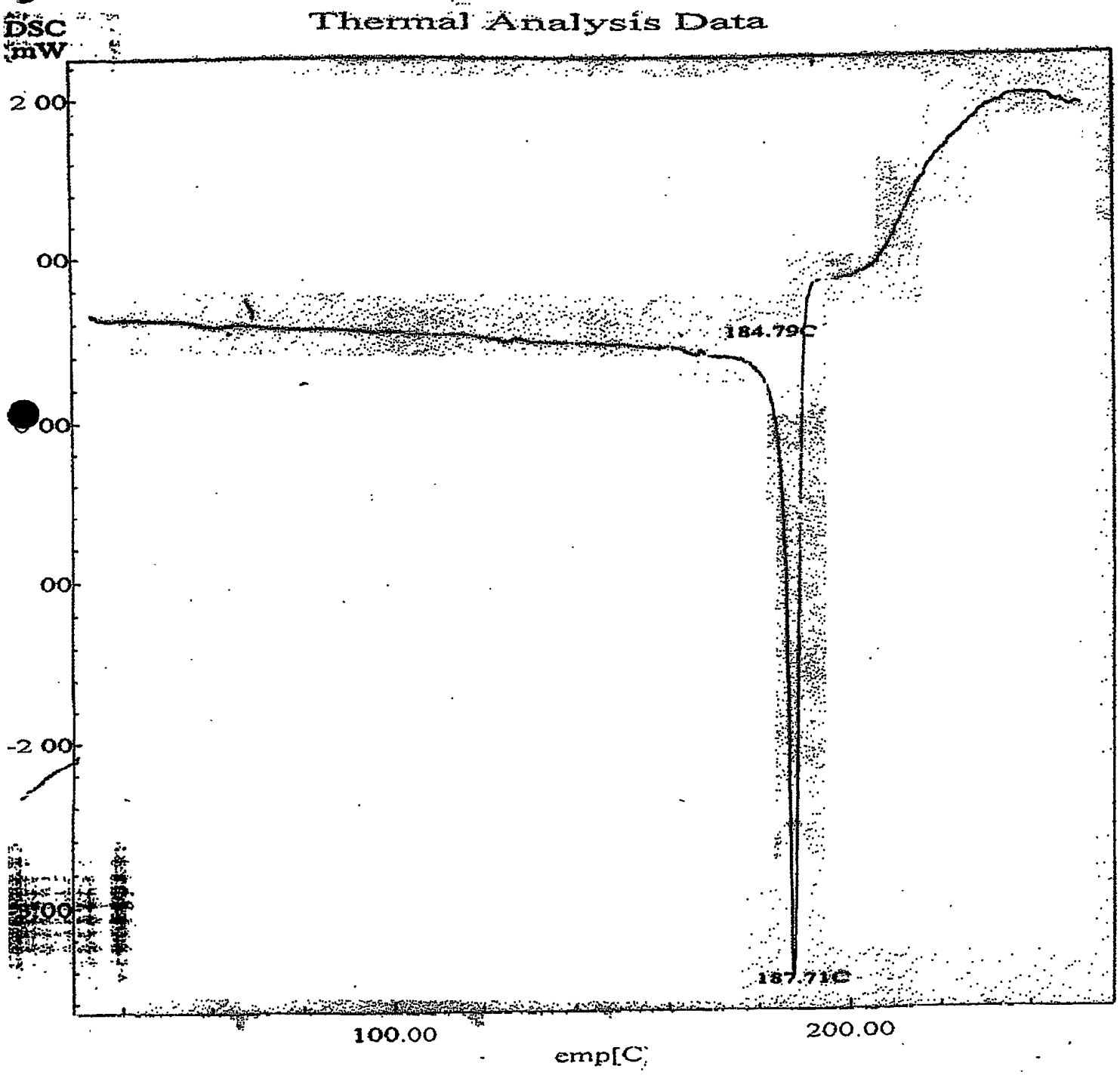
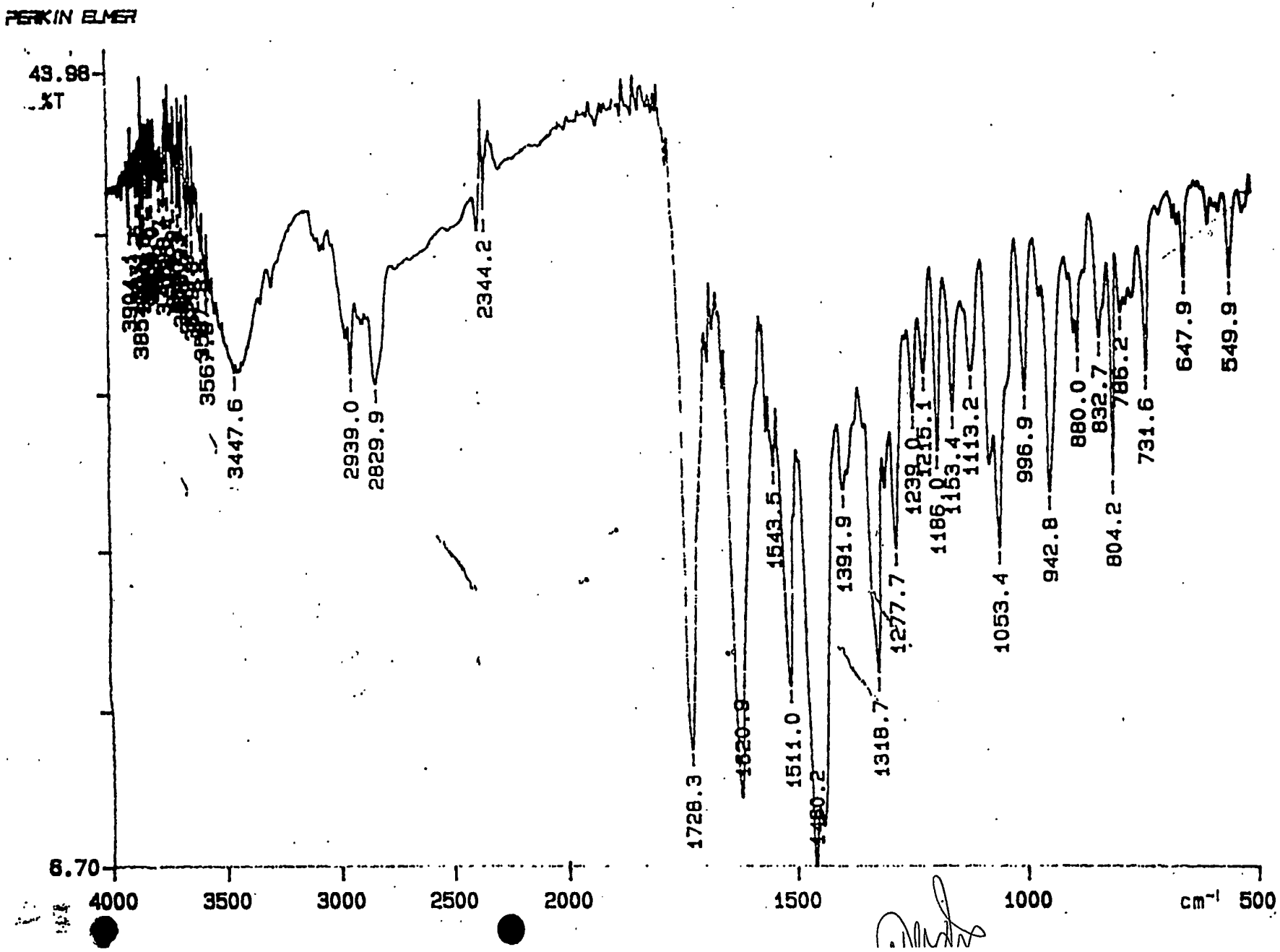


Fig. (2)

Dr. Reddy's Laboratories Limited



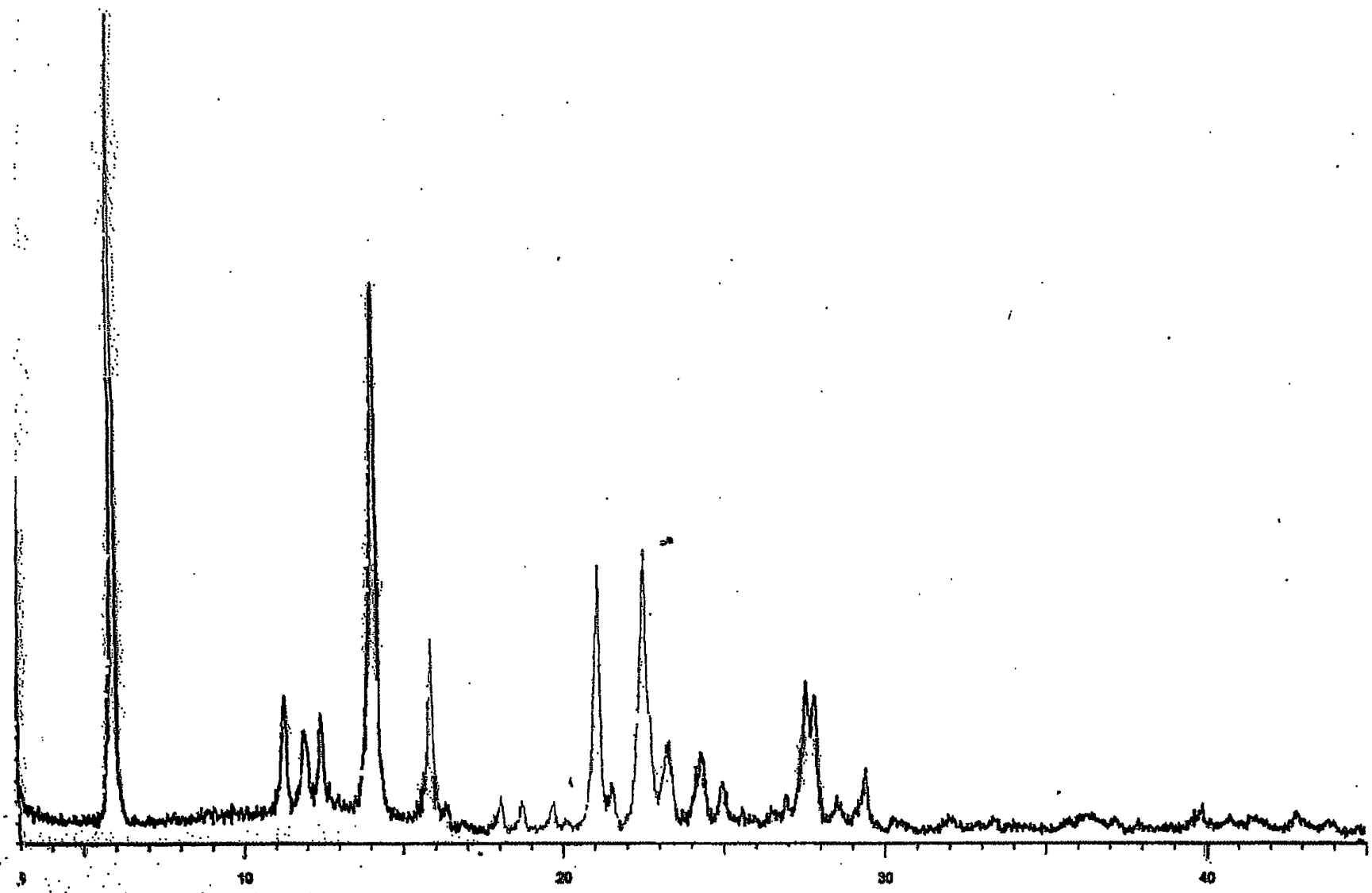


Fig. (1)